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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,027	07/30/2007	Axel Bouchon	BHC 03 2001	5506

35969 7590 03/27/2009

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
03/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,027	BOUCHON ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *5 and 17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/EP04/11008 filed 10/02/2004 which claims priority to EPO 03023288.8 filed 10/15/2003; EPO 03023287.0 filed 10/15/2003; EPO 03025573.1 filed 11/08/2003; and EPO 03025572.3 filed 11/08/2003.

Claims 1-22 are pending. Claims 5, 17-22 are withdrawn from consideration. Claims 1-4, 6-16 are under examination.

Response to Restriction/Election

2. Applicant's election of Group I and the species (Example I-12) in the reply filed on January 26, 2009 is acknowledged. The election was made with traverse, and the examiner finds the arguments unpersuasive. The traversal is on the grounds that the method claims may be reasonably searched with the compound claims since any anticipatory references or obviousness type art would reasonably be found with the search of the compounds. This is true, however the applicant should be reminded that the claims require careful consideration under all the statutes and that issues unrelated to anticipation or obviousness require extensive searching and evaluation of these various method claims. Thus the search for the method claims extends beyond these particular compounds and requires a separate search. Should the compound claims be found allowable, the method claims will be rejoined in due course. This application contains claims drawn to a nonelected invention with traverse. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Under examination

Group I, Claims 1-4, 6-16 drawn to compounds and compositions where all Q's are carbon, drawn to tetrahydronaphthalenes. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It would appear that these claims are compositions, despite the recitation of functional language "is a VR1 antagonist" "for the treatment and/or prevention of" various symptoms and disease, etc. as they are drawn to the same materials. Functional language as that of the instant claims carries no patentable weight in claims for compositions of matter see *Union Oil Co. of California v. Atlantic Richfield Co.* 54 USPQ2d 1227 where "composition claims cannot, as the appellant refiners argue, embrace only certain uses of that composition. (citing In Re Spada) Otherwise these composition claims would mutate into method claims." The scope of these claims is unclear as one cannot ascertain based on the structure of the compounds of claim 1 which materials actually meet the requirements of these various limitations. These compounds have not been evaluated for any therapeutic use. Should the applicant want to pursue method claims in this application they will be rejoined to allowable product claims. It is recommended that these claims be rewritten without intended use.

4. Claims 1-2, 6-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The reference to a "Chapter" has no antecedent basis. It is unclear what these representations mean as chemical language does not use "Chapter". Moreover the

variables are continuously redefined with these "Chapter" designations such that it is unclear what is actually being claimed.

5. Claims 1, 6-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The drawings have what is apparently an extra carbon on both the E groups and the A groups (the tetrahydronaphthylene ring). It would appear that these structures are drawn using bond line formula, where the vertex or an end of a line represents a carbon atom, and hydrogen atoms are not drawn in. The rules for drawing structures in bond line formula are outlined in most introductory texts on organic chemistry, see for instance: Johnson, A. W. Invitation to Organic Chemistry 1999 Jones and Bartlett: Mississauga, Canada, pg. 24. The number sign apparently represents a point of attachment the end of the line next to the number sign would seem to represent a carbon atom. It is unclear what rules are being used in these representations and they could be interpreted as having a carbon there or not.

6. Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 has an extra carbon atom attaching the E and A moieties to the Formula A (see rejection at 5), while the dependent claims 2-4 do not. There is a lack of antecedent basis in the claims.

Claim Rejections - 35 USC § 102

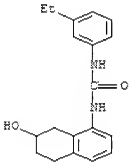
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

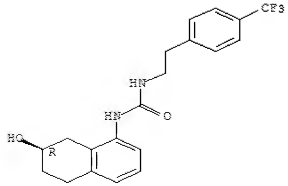
> A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-4, 6-16 are rejected under 35 U.S.C. 102(e) as being anticipated by WO03095420 (cited on the IDS, also made over the PGPub of U.S. application 10/513,848 the national stage), which has a common assignee and some common inventors with the instant application.

The WO document teaches hundreds of anticipatory compounds such as those shown below, where A is the hydroxynaphthalenes and E is various urea and amide moieties. This is essentially the genus of claims 1-4.





Claim Rejections - 35 USC § 103

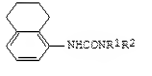
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-2, 6-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aman JP 04178362 A and Aman JP 04178363. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

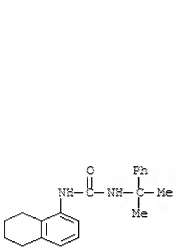
A) Aman et. al. teaches a class of compounds that are antifungals, acaricides, miticides etc. In particular the following genus of compounds:

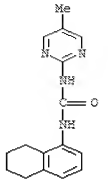


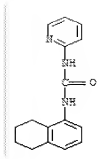
I

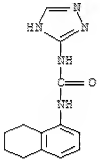
Urea derivs. I [R1 = H, lower alkyl, lower alkoxy; R2 = lower alkyl, lower alkenyl, 4-morpholinyl, {lower alkoxycarbonyl-, carbamoyl-, or arylcarbonyl-substituted} Ph, five-membered heterocyclyl, etc.]

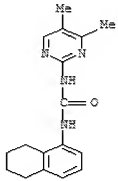
Some examples provided to support this genus are shown below:

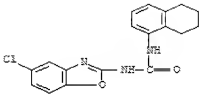


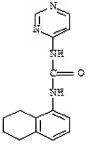


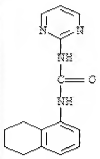


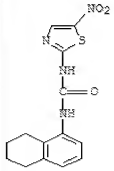


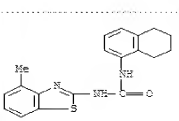


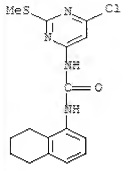
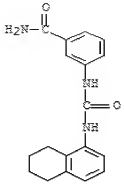
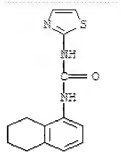
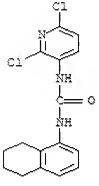
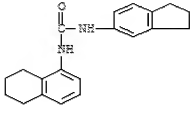
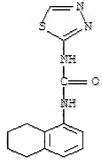
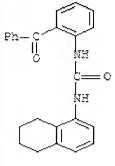
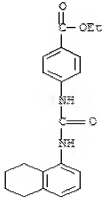
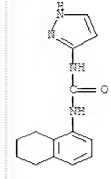


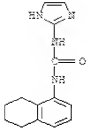


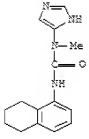


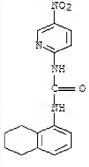










B) While the instant claims have provisoed out the prior art species the only difference at least when R^2 or R^3 is alkyl is the interchange of H for methyl.

C) The level of ordinary skill in the art is high, and would be someone with synthetic chemistry experience and biochemistry. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these analogs based on the expectation that such simple analogs would have similar properties and upon the routine nature of such experimentation.

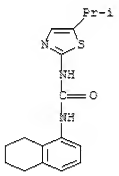
D) In at least one aspect the only difference is H vs. Me, which has long been held to be a non-patentable distinction. (See *In Re Herr* 134 USPQ 176, *In re Wood*, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lahr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963), also discussed in *In Re Paquette* 165 USPQ 317, "we also think it would be obvious to the person skilled in the art to provide dimers of an N-methyl-2-pyridone modified by the presence of a methyl substituent on one of the otherwise unsubstituted carbons of the ring. Since little could be more expected than that the resulting dimer would have two such substituents, that fact clearly does not detract from the obviousness of claims 15-18." See also *Ex parte Bluestone*, 135 USPQ 199 (Bd. Pat. App. & Int. 1961) finding that the N-methyl derivative of a prior art thiazolidinone unpatentably obvious and stated, citing *Ex parte Weston and Hamlin* with favor "A case nearly on all fours with this situation is *Ex parte Weston and Hamlin*, 121 USPQ 428 , wherein this Board held that mono substituted N' piperazines were not patentable over di-substituted piperazines of the reference because chemists are well aware of the difference between secondary and tertiary amines and their reactivities including the possibility of further substitution for the hydrogen in the secondary amine. This is the substitution that appellant has made in the Alvord compound." *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34

USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para)*. In terms of the composition claims, the compounds were dissolved in DMSO, which is a pharmaceutically acceptable solvent.

9. Claims 1, 6-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pevarello U.S. 6,863,647. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) U.S. 6,863,647 teaches a class of compounds that were useful as cdk/cyclin inhibitors, and are useful for treating cell proliferative disorders. In particular the following compound:

RN 267430-46-6 CAPLUS
CN Urea, N-[5-(1-methylethyl)-2-thiazolyl]-N'-naphthalenyl)- (CA INDEX NAME)



B) While the instant claims have provisoed out the prior art species the only difference at least when R1 or R is heteroaryl and the heteroaryl is thiazole and R^2 or R^3 is alkyl is the interchange of H for methyl.

C) The level of ordinary skill in the art is high, and would be someone with synthetic chemistry experience and biochemistry. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these analogs based on the expectation that such simple analogs would have similar properties and upon the routine nature of such experimentation.

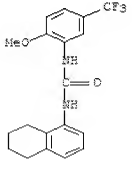
D) In at least one aspect the only difference is H vs. Me, which has long been held to be a non-patentable distinction. (See *In Re Herr* 134 USPQ 176, *In re Wood*, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lahr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963), also discussed in *In Re Paquette* 165 USPQ 317, "we also think it would be obvious to the person skilled in the art to provide dimers of an N-methyl-2-pyridone modified by the presence of a methyl substituent on one of the otherwise unsubstituted carbons of the ring. Since little could be more expected than that the resulting dimer would have two such substituents, that fact clearly does not detract from the obviousness of claims 15-18." See also *Ex parte Bluestone*, 135 USPQ 199 (Bd. Pat. App. & Int. 1961) finding that the N-methyl derivative of a prior art thiazolidinone unpatentably obvious and stated, citing *Ex parte Weston and Hamlin* with favor "A case nearly on all fours with this situation is *Ex parte Weston and Hamlin*, 121 USPQ 428 , wherein this Board held that mono substituted N' piperazines were not patentable over di-substituted piperazines of the reference because chemists are well aware of the difference between secondary and tertiary amines and their reactivities including the possibility of further substitution for the hydrogen in the secondary amine. This is the substitution that appellant has made in the Alvord compound.") *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34

USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para).* In terms of the composition claims, the compounds were tested for pharmacological activity in a pharmaceutically acceptable solvent.

10. Claims 1-3, 6-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olesen et. al. WO 9422807 AND Christophersen et. al. WO 9745111 (abstract only) in view of Patani et. al. *Chemical Reviews* 1996, 96, 3147-3176 AND Gross WO 9937607. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

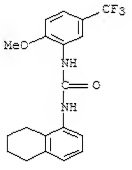
A) Olesen et. al. WO 9422807 teaches a class of compounds that were useful as ion channel inhibitors, and are useful for treating arterial hypertension, coronary artery spasms, asthma, irritable bowel syndrome, spastic bladder, ischemia, psychosis, convulsions. In particular WO 9422807 the following compound:

RN 160383-97-1 CAPLUS
CN Urea, N-[2-methoxy-5-(trifluoromethyl)phenyl]-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)- (CA INDEX NAME)

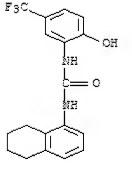


WO 9745111 teaches the following compounds:

```
IN   Urea, N-[2-methoxy-5-(trifluoromethyl)phenyl]-N'-(5,6,7,8-tetrahydro-1-
     naphthalenyl)-  (CA INDEX NAME)
```



```
RN   200267-58-9  CAPLUS
IN   Urea, N-[2-hydroxy-5-(trifluoromethyl)phenyl]-N'-(5,6,7,8-tetrahydro-1-
     naphthalenyl)-  (CA INDEX NAME)
```



B) The difference between the prior art and the instant claims is a hydroxy group.

C) The level of ordinary skill in the art is high, and would be someone with synthetic chemistry experience and familiar with biochemistry. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these analogs

based on the expectation that such simple analogs would have similar properties and upon the routine nature of such experimentation.

D) The replacement of a hydrogen atom with a hydroxy group is a well known modification in medicinal chemistry as shown by Patani Pg. 3152, at "4. Fluorine and Hydroxyl, Amino, or Methyl Groups as Replacements for Hydrogen (Grimm's Hydride Displacement Law)". Most compellingly, the Gross document show that in the field of ion channel ligand development, hydroxylation of the tetrahydronaphthalene nucleus is well known, see the entire document, the table on pg. 29 for instance. The tetrahydronaphthalene nucleus is hydroxylated in this very precise 2 position.

One would be motivated to make this change with the expectation that the compounds would be ion channel ligands and a further expectation that potency would be increased. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para).* In terms of the composition claims, the compounds were tested for pharmacological activity in a pharmaceutically acceptable solvent. Given the very close utility, structural similarity and the fact that this modification was well known in this very narrow field the conclusion of obviousness is appropriate.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-4, 6-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds where R^1, R^4, or R is phenyl, benzyl, CH_2-pydridyl, 1,3-benzodioxolyl, tetrahydronaphthalene, isoxazole, dihydroindene, thiadiazole and indole which could be substituted with halogen, CF_3, OCF_3, phenyl, pyridine, pyridyloxy, alkoxy, and alkyl, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of substituted phenyl derivatives, heterocycles, and amines bearing multiple substitutions of an unascertainable scope see 112 2nd rejection above. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. In addition these compounds are claimed to be used as drugs. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist who would make the compounds. **(C) The state of the prior art: (E) The**

level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:

The applicant has given the public little guidance as to what the requirements of activity for these compounds might be. The sole statement we are given: "For practical reasons, the compounds are grouped in four classes of activity as follows: IC50- A < or = 0.11μM B < or = 0.5μM C < or = ~ 1μM < D." It is known that structural requirements exist for TRPV1 ligands. In a similar class of compounds substitution of *t*-Bu on an aromatic ring adjacent to the amide with OMe had a 1000 fold decrease in activity (Michele C. Jetter, Mark A. Youngman, James J. McNally, Sui-Po Zhang, Adrienne E. Dubin, Nadia Nasserb and Scott L. Dax, "N-Isoquinolin-5-yl-N0-aralkyl-urea and –amide antagonists of human vanilloid receptor 1 *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 3053–3056; Table 1, compare **7l** to **7n**). Thus electron withdrawing or at least lipophilic groups seem to be required for activity. The compounds of broad claims of 1-4, 6-16, would not work as antagonists.

More informatively, a large SAR study was done on TRPV1 antagonist remarkably similar to the compounds of the instant case, which no doubt benefited the design of the instant invention, Swanson et. al. "Identification and Biological Evaluation of 4-(3-Trifluoromethylpyridin-2-yl)piperazine-1-carboxylic Acid (5-Trifluoromethylpyridin-2-yl)amide, a High Affinity TRPV1 (VR1) Vanilloid Receptor Antagonist" *Journal of Medicinal Chemistry* **2005**, 48, 1857-1872. In this study it was found that the heterocyclic moiety must be a piperidine, or piperazine:

> "The first library (Figure 1) demonstrated the desirability of an electron-withdrawing group in the para position of the aniline fragment for antagonist

activity and suggested that 3-substituted pyridin-2- ylpiperazines were favored. In the second library (Figure 2) which contained no 3-substituted pyridines only low affinity agonists and antagonists were obtained. The third library (Figure 3) was most informative and clearly demonstrated the importance of a 3-substituted pyridin- 2-ylpiperazine (3-Cl, 3-CH3, and 3-CF3) and a *p*-trifluoromethyl group in the aniline fragment. A fourth library, not shown, prepared from aliphatic isocyanates and 3-substituted pyridin-2-ylpiperazines afforded only inactive compounds, suggesting the need for an aromatic urea. With the intrinsic activity of the pyridinylpiperazine template confirmed, we turned our attention to a more thorough investigation of SAR at the human receptor via targeted synthesis. To this end, specific changes to the pyridine, piperazine, and aniline fragments were made. When the pyridine point of attachment was examined, 17 and 18, it was immediately apparent that the pyridin-2-ylpiperazine was optimal. A range of modifications to or replacements for the piperazine (20-26) showed that the piperazine ring was tolerant of small substituents (e.g. 20) but further substitution (21-23), ring expansion (24) or replacement with 3-aminopyrrolidine (25) or 4-aminopiperidine (26) afforded considerably less active compounds. Removal of a single piperazine nitrogen (27 and 28), using the chemistry of Scheme 2, afforded a less active compound as did removal of both a piperazine and the pyridine nitrogens, using the chemistry of Scheme 3 (29 and 30)."

Compounds 23 and 25, are inactive, not less active, but inactive.

Table 1. Potency at Recombinant TRPV1[a]

compd	human EC_{50} (nM)	efficacy (%)	human IC_{50} (nM)	SEM (n)	rat EC_{50} (nM)	efficacy (%)	rat IC_{50} (nM)
23			>10000	(3)			>10000
25	>10000, IA[b]		>10000	(3)			13100

What are the important structural features for the claimed utility? The compounds that were prepared at least, a lipophilic substituents of limited size were used at R1 R, and R4 in addition In this case the claimed compounds bear little structural resemblance to one the ones actually prepared.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make or use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-4, 6-16 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-18 of copending Application No. 10/513,848. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The species appear to be the same, see the 102(e) rejection above for some examples of the hundreds of species.

13. Claims 1-4, 6-16 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-11 of copending Application No. 10/578,490. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The species also appear to be the same or very minor variants.

14. Claims 1-4, 6-16 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-5, 27-28 of copending Application No. 10/537,217. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The species also appear to be the same or very minor variants.

15. Claims 1-4, 6-16 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-8 of U.S. 7,381,840.

The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The species also appear to be the same or very minor variants.

Conclusion

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625